08-16-06

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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Application Number | 09/991,150 |
| Filing Date | November 16, 2001 |
| First Named Inventor | Baker, et al. |
| Group/Art Unit | 1646 |
| Examiner Name | Kemmerer, Elizabeth |
| Total Number of Pages in This Submission | |
| Attorney Docket Number | 39780-2730P1C48 |

**ENCLOSURES** *(check all that apply)*

- ☒ **FEE TRANSMITTAL FORM**
  - ☐ Fee Attached
- ☐ Amendment / Response
  - ☐ After Final
  - ☐ Version with Markings Showing Changes
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Small Entity Statement
- ☐ Request for Refund
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ **APPEAL COMMUNICATION TO GROUP** *(Appeal Notice, Brief, Reply Brief)*
- ☒ **REQUEST FOR ORAL HEARING**
- ☐ Status Letter
- ☒ **ADDITIONAL ENCLOSURE(S)** *(please identify below):*
  - **STAMPED RETURN POSTCARD**

Remarks

**AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT 08-1641 FOR ANY FEES DUE IN CONNECTION WITH THIS PAPER (Ref. Atty. DOcket No. 39780-2730P1C48).**

**SIGNATURE OF APPLICANT, ATTORNEY OR AGENT**

| | | | |
|---|---|---|---|
| Firm *or* Individual name | **GINGER R. DREGER, ESQ., REG. NO. 33,055**, HELLER EHRMAN LLP | | |
| Signature | | | |
| Date | **AUGUST 14, 2006** | Customer Number: | **35489** |

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| Signature | C. Rogers | Date | **AUGUST 14, 2006** |

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# COMBINED FEE TRANSMITTAL for FY 2006

*Effective 12/08/2004. Patent fees are subject to annual revision.*

PTO/SB/17 (12-04 Revised) (For payment of 37 CFR 1.17 fees including (f), (g), (h), & (i))

☐ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** | **($) 1,000.00**

| *Complete if Known* | |
|---|---|
| Application Number | 09/991,150 |
| Filing Date | November 16, 2001 |
| First Named Inventor | Baker, et al. |
| Examiner Name | Kemmerer, Elizabeth |
| Art Unit | 1646 |
| Attorney Docket No. | 39780-2730P1C48 |

## METHOD OF PAYMENT (check one)

| ☐ Check | ☐ Credit card | ☐ Money Order | ☐ Other | ☐ None |
|---|---|---|---|---|
| ☒ Deposit Account | | | | |

Deposit Account Number: 08-1641 (Ref. Atty. Docket No. 39780-2730P1C48)

Deposit Account Name: Heller Ehrman LLP

**The Commissioner is authorized to:** *(check all that apply)*

☒ Charge fee(s) indicated below

☒ Credit any overpayments and charge any deficiencies

☒ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the deposit account

## FEE CALCULATION

### 1. BASIC FILING, SEARCH, AND EXAMINATION FEES

| Application Type | FILING FEES Entity Fee ($) | FILING FEES Small Entity Fee ($) | SEARCH FEES Entity Fee ($) | SEARCH FEES Small Entity Fee ($) | EXAMINATION FEES Entity Fee ($) | EXAMINATION FEES Small Entity Fee ($) | Fees Paid ($) |
|---|---|---|---|---|---|---|---|
| Utility | 300 | 150 | 500 | 250 | 200 | 100 | |
| Design | 200 | 100 | 100 | 50 | 135 | 65 | |
| Plant | 200 | 100 | 300 | 150 | 160 | 80 | |
| Reissue | 300 | 150 | 500 | 250 | 600 | 300 | |
| Provisional | 200 | 100 | 0 | 0 | 0 | 0 | |

**SUBTOTAL (1)** $ 0

### 2. EXTRA CLAIM FEES

| Entity Fee ($) | Small Entity Fee ($) | Fee Description |
|---|---|---|
| 50 | 25 | Each claim in excess of 20 or, for Reissues, each claim in excess of 20 and more than in the original patent |
| 200 | 100 | Each Independent claim in excess of 3 or, for Reissues, each independent claim more than in the original patent |
| 360 | 180 | Multiple dependent claim, if not already paid |

| | | | Extra Claims | | Fee from above | | Fee Paid |
|---|---|---|---|---|---|---|---|
| Total Claims | | -20** = | | x | | = | |
| Independent Claims | | -3** = | | x | | = | |

***or number previously paid, if greater; For Reissues see below*

Multiple Dependent | = |

**SUBTOTAL (2)** $ 0

### 3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof (round up to the a whole number). See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s)

| Total Sheets | | Extra Sheets | | Number of each additional 50 | Fee ($) | | Small Entity Fee ($) |
|---|---|---|---|---|---|---|---|
| | -100 = | | /50 = | | x 250 | OR | x 125 |

**SUBTOTAL (3)** $ 0

## FEE CALCULATION (continued)

**4. PETITION FEES UNDER 37 CFR 1.17 (f)** — Fee Paid

Fee Code: 1462 **Fee $ 400** For petitions filed under: § 1.53(e); § 1.57(a); § 1.182; § 1.183; § 1.378(e); § 1.741(b)

**5. PETITION FEES UNDER 37 CFR 1.17 (g)** — Fee Paid

Fee Code: 1463 **Fee $ 200** For petitions filed under: § 1.12; § 1.14; § 1.47; § 1.59; § 1.103(a); § 1.136(b); § 1.295; § 1.296; § 1.377; § 1.550(c); § 1.956; § 5.12; § 5.15; § 5.25

**6. PETITION FEES UNDER 37 CFR 1.17 (h)** — Fee Paid

Fee Code: 1464 **Fee $ 130** For petitions filed under: § 1.19(g); § 1.84; § 1.91; § 1.102(d); § 1.138(c); § 1.313; § 1.314

**7. PROCESSING FEES UNDER 37 CFR 1.17 (i)** — Fee Paid

Fee Code: 1808 (1803 for § 1.221) **Fee $ 130** For petitions filed under: § 1.28(c)(3); § 1.41; § 1.48; § 1.52(d); § 1.53(b)(3); § 1.55; § 1.99(e); § 1.103(b); § 1.103(c); § 1.103(d); § 1.217; § 1.221; § 1.291(c)(5); § 1.497(d); § 3.81

### 8. OTHER FEES

| Entity Fee ($) | Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|
| 130 | 65 | Surcharge - late filing fee or oath | |
| 50 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 130 | 130 | Non-English specification | |
| 2,520 | 2,520 | For filing a request for *ex parte* reexamination | |
| 920* | 920* | Requesting publication of SIR prior to Examiner action | |
| 1,840* | 1,840* | Requesting publication of SIR after Examiner action | |
| 120 | 60 | Extension for reply within first month | |
| 450 | 225 | Extension for reply within second month | |
| 1,020 | 510 | Extension for reply within third month | |
| 1,590 | 795 | Extension for reply within fourth month | |
| 2,160 | 1,080 | Extension for reply within fifth month | |
| 500 | 250 | Filing a brief in support of an appeal | |
| 790 | 395 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 1,510 | 1,510 | Petition to institute a public use proceeding | |
| 500 | 250 | Petition to revive - unavoidably abandoned application | |
| 1,500 | 750 | Petition to revive - unintentionally abandoned application | |
| 50 | 50 | Processing fee for provisional appls (37 CFR 1.17(q)) | |
| 180 | 180 | Submission of Information Disclosure Statement | |
| 1,000 | 500 | Request for oral hearing | 1,000.00 |
| 790 | 395 | For each additional invention to be examined (37 CFR 1.129(b)) | |
| 790 | 395 | Request for Continued Examination (RCE) | |
| 900 | 900 | Request for expedited examination of a design application | |

Other fee (specify)

**SUBTOTAL (4+5+6+7+8)** **$1,000.00**

* Reduced by Basic Filing Fee Paid

## SUBMITTED BY

| Name *(Print/Type)* | GINGER R. DREGER, ESQ. | Registration No. *(Attorney/Agent)* | 33,055 | Complete *(if applicable)* Telephone | 650 324-7000 |
|---|---|---|---|---|---|
| *Signature* | | *Date* | AUGUST 14, 2006 | Customer No. | 35489 |

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | ) Examiner: Kemmerer, Elizabeth |
| Kevin P. BAKER, *et al.* | ) Art Unit: 1646 |
| Application Serial No. 09/991,150 | ) Confirmation No: 4272 |
| Filed: November 16, 2001 | ) Attorney's Docket No. 39780-2730 P1C48 |
| For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME** | ) **Customer No. 35489** |

**EXPRESS MAIL LABEL NO.: EV 765 978 205 US**
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**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES**
**APPELLANTS' REPLY BRIEF**

**MAIL STOP: APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On September 16, 2004, the Examiner made a final rejection to pending Claims 124, 129-131 and 135-145. A Notice of Appeal was filed on January 27, 2005, an Appeal Brief was filed on July 26, 2005 and an amended Appeal Brief was filed on April 3, 2006.

An Examiner's Answer was mailed June 12, 2006. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

## ARGUMENTS

***Claim Rejections Under 35 U.S.C. §101 and § 112, First Paragraph***

Concerning the rejection of Claims 124, 129-131 and 135-145 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in her Answer, the Examiner argues that "a slight amplification of a gene does not necessarily mean that the nucleic acid is a cancer marker." The Examiner cites the following arguments in support of this conclusion:

(1) The specification shows that PRO341 genomic DNA was amplified in only three out of fourteen lung tumor samples as compared to normal human DNA control that was apparently isolated from blood. One skilled in the art would conclude that it was more likely than not that PRO341 genomic DNA is *not* amplified in any given lung tumor sample based on those results (emphasis in original; page 6, last two lines through page 7, line 4 of the Examiner's answer).

(2) Even if the data demonstrated a slight increase in copy number of PRO341 genomic DNA in primary tumors, such would not be indicative of a use of the claimed nucleic acids as diagnostic agents, since: (a) cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes allegedly, according to Sen (2000); (b) the data are not corrected for aneuploidy, (c) Hittelman (2001) teaches that precancerous lung epithelium is often aneuploid (page 4, line 15 to of the Examiner's Answer). The Examiner adds that, while it might be argued in hindsight that PRO341 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is **not well-established in the prior art**." (emphasis added; page 5, line 13-16 of the Examiner's answer).

(3) Referring to three publications Livak *et al.*, Heid *et al.* and Pennica *et al.* cited in the Goddard Declaration, the Examiner says that "none of Livak *et al.*, Heid *et al.*, nor Pennica *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors" (page 10, line 17 of the Examiner's Answer).

The same arguments are cited in support of the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement for how to use the invention.

The Examiner's arguments will be addressed in the order they are listed above.

**Arguments**

(1) In making the rejection that "only three out of fourteen lung tumor samples tested positive", the Examiner seems to indicate that a tumor marker is patentable only if the marker tests positive in a statistically high number of samples compared to the total number of samples tested or if the tumor tests positive in every tissue type that was studied. However, this is legally incorrect. Neither the M.P.E.P. nor the Utility Guidelines require that it is necessary for the Appellant to show a positive result in most or a larger percentage of the tissue samples studied in order to make an assertion of utility, nor are they needed to show that the tumor marker identifies cancers of various tissues types, *e.g.,*: lung, colon, etc. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO341 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Furthermore, as indicated previously, it is well-accepted in the art that not all tumor markers are generally associated with every tumor or every tumor type, or even, with most tumors or most tumor types. In fact, some tumor markers are useful for identifying rare malignancies. That is, even if the association of a tumor marker with a particular type of tumor lesion is rare, or, even if the occurrence of a particular kind of tumor lesion itself is rare, since such markers identifying rare tumors, they have great value in tumor diagnosis, and

consequently, in tumor prognosis. The ΔCt values for PRO341 of at least 1.12-1.33 ΔCt units, which correspond to $2^{1.12}$ -$2^{1.33}$- fold amplification or 2.173 to 2.514 fold amplification in primary lung tumors, were considered significant according to the Goddard declaration. The skilled artisan would know the value and utility of rare tumor markers. Therefore, this rejection should be withdrawn.

(2) Appellants had discussed the Examiner's point on aneuploidy and the Hittelman reference in detail in their Appeal brief filed July 26, 2005 and amended Appeal brief filed April 3, 2006. Appellants had submitted that even if the observed gene amplification for PRO341 were due to aneuploidy (which Appellants do not concede to), since aneuploidy itself is associated with early detection of cancer, the PRO341 gene would still be useful as a biomarker, and this view is well-supported by the teachings of references in the art like the Examiner's cited references Sen *et al.* and Hittelman. Hittelman clearly teaches on page 2, fourth paragraph, line 3 "it is important to identify individuals **at significantly increased cancer risk** who might best benefit from different types of intervention(emphasis added)." However, the Examiner indicates that, that 'a marker is useful for precancerous or damaged lung epithelium' is not available in the Appellants' specification as filed. Appellants point out that, this point was well-established in the prior art, at the effective date of filing of this application, contrary to what the Examiner contends. Appellants submit that there was a shift towards detecting pre-malignant and early-malignant lesions of lung and associating aneuploidy, precancerous lung or damaged lung epithelium and early lung cancer detection in the prior art. For instance, it was known that lung cancer was the end-stage of multi-step carcinogenesis, and in most cases, was driven by genetic and epigenetic damage caused by chronic exposure to tobacco carcinogens. It was also known that preneoplastic cells contained several molecular genetic abnormalities identical to those found in overt lung cancer cells, and well before the effective filing date of **July 9, 1998** of the present application, the therapeutic paradigm and focus had already shifted from targeting only clinically verified lung cancer toward targeting pre-malignant and early-malignant lesions. Furthermore, the prospects of lung cancer screening had become more meaningful as a consequence of developments in biology and radiology and better possibilities to define high risk populations most suitable for lung cancer screening. Articles in lung cancer and early- lung cancer detection

published around and before July 9, 1998 collectively lent support to the view that it was important to detect, diagnosis and treat early lung cancer. Therefore, one skilled in the art of oncology, at the effective date of filing of the instant application, would have known, based on the teachings of the instant specification and the well-established art in the lung cancer, how to use the instant PRO341 gene for the diagnosis of certain lung cancers, without undue experimentation.

(3) The Examiner says that "none of Livak *et al.*, Heid *et al.*, nor Pennica *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors" in rejecting the Goddard Declaration. Appellants strongly disagree. The above references were cited in the Goddard Declaration to show that quantitative TaqMan PCR assay is a well-known and widely used assay in the art for studying gene amplification in various cancers. For instance, the Goddard declaration clearly says:

> "the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer."

Therefore, Dr. Goddard did not rely on the above mentioned references for determining whether "a 2-fold amplification is significant." The Examiner has misrepresented of the actual purpose for presenting these references in the Goddard Declaration. Instead, the opinions expressed in the Goddard Declaration regarding the significance of the 2-fold amplification are based on Dr. Goddard's own personal scientific experience and factual findings. By making this rejection, the Examiner seems to disregard an expert's statements and conclusions based on the Examiner's own personal disagreement over the significance or meaning of the facts offered, without solid support or scientific showing for her opinion(s). Appellants respectfully remind the Examiner that the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states, "Office personnel must accept an opinion from a qualified expert that is based upon

relevant facts whose accuracy is not being questioned; **it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered"** (emphasis added). Therefore, barring solid scientific evidence from the art as that show why a 2-fold amplification of DNA in the TaqMan PCR assay would not be considered significant by one skilled in the art, the basis for this utility rejection is flawed and is inappropriate.

For the reasons given above, Appellants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the rejections in the Examiner's answer and therefore, the Patent Office has failed to meet its initial burden of proof. Accordingly, this rejection under 35 U.S.C. §101 and §112, first paragraph should be withdrawn.

## CONCLUSION

For the reasons given above, Appellants submit that the gene amplification assay disclosed in Example 170 of the specification, and the advanced state of the art in oncology, provide at least one patentable utility for the PRO341 nucleic acids of Claims 124, 129-131 and 135-145, and that one of ordinary skill in the art would understand how to use the claimed polypeptides and would have found such testing routine and not 'undue.' Therefore, Claims 124, 129-131 and 135-145 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C48**).

Respectfully submitted,

Date: August 14, 2006

Ginger R. Dreger
Reg. No. 33,055

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